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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,108	07/17/2003	Richard S. Blumberg	S1383.70011.US00	5945

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Alan W. Steele
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,108	BLUMBERG ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,18,23,28,33,40,47 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, 18, 23, 28, 33, 40, 47, and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was filed 2/21/06.

Claims 1-13, 18, 23, 28, 33, 40, 47, and 49 remain pending and are under consideration in this Office Action.

Information disclosure statements were filed on 12/1/03, 10/8/04, and 11/17/04. However, the Examiner could not locate a form 1449, or facsimile, connected with the 10/8/04 submission. In the response filed 2/21/06, Applicant indicated that no form 1449 was filed on 10/8/04, but an International Preliminary Examination Report was filed on that date. This document has been considered.

Drawings

Seventeen sheets of drawings were filed with the application. Formal Drawings of Figs 5, 6, and 9-13 were received on 10/23/05. The drawings are acceptable for examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5, and 7-12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chang (US Patent 5,723,125) in view of any one of Carozzi et al (US

Patent 5,686,600), Dillon et al (US Patent 5,395,750), or Pastan et al (US Patent 5,990,296).

Chang taught a fusion protein comprising a human interferon alpha, such as IFN alpha 2a or 2b, joined at its C-terminus, via a flexible linker, to the N-terminus of a human gamma immunoglobulin Fc fragment, wherein the linker had the sequence $G_2SG_2SG_4SG_4S$. This linker peptide was designed to increase the flexibility between the two moieties and thus maintain their biological activity. See abstract, column 3, lines 1-11 and 54-56, and column 6, lines 16, 17, and 42-47. The fusion protein formed a homodimer under non-reducing conditions. See column 7, lines 21-27.

Chang did not teach a $(GGGGS)_2$ linker a $(GGGGS)_3$ or a $(GGGGS)_4$ linker.

Carozzi and Dillon taught $(GGGGS)_2$ and $(GGGGS)_3$ linkers, respectively, in the fusion of antibody heavy chains to antibody light chains (Carozzi and Dillon), and Pastan taught the use of a $(GGGGS)_4$ linker in the fusion of an immunoglobulin variable region and a cytotoxin. See Carozzi at column 18, lines 49-65 , Dillon at Fig. 2 and paragraph bridging columns 8 and 9, and Pastan at column 4, lines 20-25.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute one of the $(GGGGS)_2$ linker a $(GGGGS)_3$ or a $(GGGGS)_4$ linkers for the linker of Chang because all of these linkers are flexible glycine-serine linkers such as were recognized in the art to facilitate folding and production of the fusion proteins. See e.g. Carozzi at column 5, lines 4-9. Furthermore, as flexible linker molecules, they fulfill the same function and would be recognized in the art as exchangeable equivalents, absent some evidence of a difference that would critically

affect their function in the claimed invention. The use of any one of these linkers in a fusion protein would be obvious in view of the use of any of the others because they all have the same art recognized function, similar structural characteristics, and are all used for the same purpose.

Claim 5 is included in this rejection because the Fc gamma4 region of Chang (depicted by residues 205-433 of SEQ ID NO:7) comprises many sequences provided by instant SEQ ID NO:2, e.g. PPCP at residues 210-213 of Chang and residues 7-10 of instant SEQ ID NO:2 and LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS at residues 221-253 of Chang and residues 15-47 instant SEQ ID NO:2.

Claim 3 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Chang in view of any one of Carozzi et al (US Patent 5,686,600), Dillon et al (US Patent 5,395,750), or Pastan et al (US Patent 5,990,296) as applied to claims 1, 2, 5, and 7-12 above, and further in view of Tovey (US Patent 6,207,145).

The teachings of Chang, Carozzi, Dillon , and Pastan are summarized above and can be combined to render obvious a fusion protein comprising IFN alpha 2a or 2b comprising an immunoglobulin Fc region attached to the C-terminus of the interferon moiety.

These references did not teach a "consensus" interferon.

Tovey taught a consensus interferon that has higher activity than IFN alpha 2a or 2b. See column 1, lines 37-45. In view of this advantage, it would have been

obvious to one of ordinary skill in the art at the time of the invention to substitute the consensus IFN alpha of Tovey for the IFN alpha 2a or 2b of Chang.

Claims 4 and 6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chang in view of any one of Carozzi et al (US Patent 5,686,600), Dillon et al (US Patent 5,395,750, or Pastan et al (US Patent 5,990,296) as applied to claims 1, 2, 5, and 7-12 above, and further in view of Lo et al (US Patent 5,726,044).

The teachings of Chang, Carozzi, Dillon , and Pastan are summarized above and can be combined to render obvious a fusion protein comprising IFN alpha 2a or 2b comprising an immunoglobulin human Fc gamma 4 region attached to the C-terminus of the interferon moiety.

These references did not teach an immunoglobulin Fc gamma1 region.

Lo taught that in fusion proteins comprising an immunoglobulin Fc region and a protein of interest, the Fc gamma1 region was preferred, but the gamma2, gamma3, and gamma4 regions would function equally well. See column 8, lines 7-16 . As a result it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the Fc gamma1 region of Lo for the gamma4 region of Chang because Lo indicated that these are considered to be interchangeable equivalents. Lo also indicated that the gamma1 chain conferred longer serum half life, was well characterized and is efficiently secreted from most cell types, providing additional motivation for its selection as a fusion partner. See column 3, lines 6-9 and column 8, lines 7-10.

Claims 1, 13, 23, 33, and 47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Daugherty (US Patent 6,402,733) in view of Chang taken with any one of Carozzi et al (US Patent 5,686,600), Dillon et al (US Patent 5,395,750), or Pastan et al (US Patent 5,990,296).

Daugherty taught a method for sustained systemic polypeptide delivery to a patient by aerosol administration of polypeptides such as interferon alpha. See abstract, and column 4, lines 12 and 13. The mean diameter of the particles is generally in the range of .5-4 microns. See claim 2. Daugherty also taught an aerosol delivery system capable of generating and delivering particles in the range of 0.5-4 micron. See column 5, line 55 to column 6, line 20.

Daugherty did not teach an IFN-alpha fusion protein, and was silent as to the desired central lung zone/peripheral lung zone deposition ratio.

The teachings of Chang, Carozzi, Dillon, and Pastan are summarized above and can be combined to render obvious a fusion protein comprising IFN alpha 2a or 2b comprising an immunoglobulin human Fc gamma 4 region attached to the C-terminus of the interferon moiety. The fusion protein has a higher half life in circulation than does IFN alpha.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the IFN alpha fusion protein of Chang, as modified by one of Carozzi, Dillon, and Pastan, for the IFN alpha of Daugherty. One world have

been motivated to do so because the fusion protein of Chang has a much longer half life in vivo than the native IFN alpha. See column 3, lines 15 and 16.

Note that instant claims 23 and 33 require a mass median aerodynamic diameter of at least 3 microns. This is considered to be obvious because Daugherty taught an overlapping range of particles, (0.5-4 microns). Instant claims 13 and 18 require a central lung zone/peripheral lung zone deposition ratio (C/P ratio) of at least 0.7. While Daugherty is silent as to this ratio, but absent evidence to the contrary, it would be obvious to use a C/P of 0.7 because this ratio is related to the size of the aerosol particles, and Daugherty the use of particles as large as 4 microns for delivery to alveoli. See column 3, lines 4-14, and claim 1. Note that the instant specification provides evidence that typical C/P ratios for use in alveolar targeting are in the range of 0.45-0.74. See page 26 lines 1-5 and 17-26. So, it appears that the typical usage of Daugherty overlaps the claimed C/P ratio.

Claims 11, 18, 28, 40, and 49 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Daugherty (US Patent 6,402,733) in view of Chang taken with Dillon et al (US Patent 5,395,750) and Lo et al (US Patent 5,726,044).

The teachings of Daugherty, Chang, and Dillon are summarized above. These references render obvious methods of systemic delivery of an interferon alpha 2b fusion protein comprising a C-terminal human Fc region.

The combined references do not teach an immunoglobulin Fc gamma1 region.

Lo taught that in fusion proteins comprising an immunoglobulin Fc region and a protein of interest, the Fc gamma1 region was preferred, but the gamma2, gamma3, and gamma4 regions would function equally well. See column 8, lines 7-16 . As a result it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the Fc gamma1 region of Lo for the gamma4 region of Chang because Lo indicated that these are considered to be interchangeable equivalents. Lo also indicated that the gamma1 chain conferred longer serum half life, was well characterized and is efficiently secreted from most cell types, providing additional motivation for its selection as a fusion partner. See column 3, lines 6-9 and column 8, lines 7-10.

Response to Arguments

Applicant's arguments filed 2/21/06 have been fully considered but they are not persuasive.

Applicant argues at pages 7 and 8 of the response that there is no teaching, suggestion, or motivation to modify the disclosure of Chang as suggested by the Examiner. Applicant argues that the linkers taught by Chang, Carozzi, Dillon, and Pastan are not interchangeable because the linkers of Carozzi, Dillon, and Pastan are used for a purpose that is different from the purpose of the linker in Chang, i.e. to link V_H and V_L immunoglobulin polypeptides to form single chain antibodies. Applicant argues that the requirements for a peptide linker joining functionally unrelated proteins, such as

IFN alpha and an Fc gamma chain, cannot be predicted from the disclosure of Carozzi, Chang, or Dillon.

This is unpersuasive because the linkers of Chang, Carozzi, Dillon, and Pastan are all structurally similar and were all used for a similar purpose, i.e. to join peptides via a flexible connection that allowed each to maintain its biological activity. Chang taught that the $G_2SG_2SG_4SG_4S$ linker was designed to increase the flexibility between IFN alpha and Fc gamma moieties and thus maintain their biological activity. See abstract, column 3, lines 1-11 and 54-56, and column 6, lines 16, 17, and 42-47. Carozzi taught that linkers used to join V_H and V_L moieties are also characterized by flexibility. See column 5, lines 4-6. Those of ordinary skill in the art recognize that glycine residues increase the flexibility of peptides because they lack a side chain, thereby increasing the freedom of rotation about the alpha carbons. As a result, one of ordinary skill in the art would recognize that the highly structurally similar linkers of Chang, Carozzi, Dillon, and Pastan all have a similar function, i.e. to form a flexible connection between functional peptides. Note that the instantly claimed G_4SG_4S linker taught by both Carozzi and Dillon is actually comprised within the linker of Chang. It is clear that the G_4S-based linkers of Carozzi, Dillon, and Pastan are structural and functional analogs of the flexible glycine-rich linker of Chang, and one of ordinary skill in the art would expect to be able to use them interchangeably based on their related structures and common function. Absent evidence of unexpected results, substitution of the $G_2SG_2SG_4SG_4S$ linker of Chang by linkers that are structurally and functionally related to it would be obvious.

Applicant argues at page 8 of the response that there would be no reasonable expectation of success in arriving at the claimed invention, due to the disparate nature of the components joined by the linkers. This argument is unpersuasive in view of the fact that Chang joined the exact same components using a linker ($G_2SG_2SG_4SG_4S$) that actually comprises one of the claimed linkers (G_4SG_4S). Applicant has failed to indicate exactly why one of ordinary skill in the art would expect the addition of further flexibility enhancing residues (G_2SG_2S) to the claimed G_4SG_4S linker to render the outcome unpredictable. It is important to note that the linker is not required to position the two joined moieties in any precise structural arrangement such might be required to form an enzyme active site. All that is required is the preservation of the independent function of each moiety. The prior art indicates that this can be achieved through the use of a flexible linker. See Chang above.

Applicant argues at page 9 of the response that Pastan teaches away from the instant invention by making a distinction between linkers and connectors, relying for support on column 3, lines 28-35, column 4, lines 20-25, column 13, lines 35-39 and 45-47, and Fig. 1B of Pastan. Applicant argues that Pastan taught the use of a G_4S-based linker to separate immunoglobulin heavy and light chains, but used a "connector" (SGGPEGGS) to add another functional moiety (e.g. a cytotoxic moiety) to the immunoglobulin portion. This is unpersuasive because Pastan never teaches that one should not use a G_4S-based linker to join another functional moiety to the immunoglobulin portion. The SGGPEGGS "connector" is in fact a glycine-rich peptide of slightly less flexibility (due to the inclusion of a proline residue) than the linkers

discussed above. The fact that another glycine-rich peptide was used to join functionally distinct peptide moieties certainly does not constitute teaching away from the instant invention, but instead demonstrates the obviousness of using flexible linkers or connectors, regardless of their precise sequence. For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635